REMARKS

1. History/Elections

Applicants would like to thank the Examiner for the telephone conference on July 27, 2005. During that conference, Applicants elected the breast cancer cell from Group A, and further elected modified LDL from Group B in response to the outstanding election. Applicants hereby affirm the elections made to the Examiner during the conference.

The outstanding issues are addressed individually below.

2. Claim Rejections under § 102(b)

Claims 1, 2-4 and 8 were rejected as allegedly being anticipated by Meschini *et al.* (2000) *Int. J. Cancer* 87: 615-628. The Examiner alleges that the Meschini reference discloses (1) the detection of cell *surface-expressed* vimentin using immunofluorescence as a detection means, and (2) the comparison of the level of expression of cell *surface-expressed* vimentin in drug-resistant cells to the level of expression of cell *surface-expressed* vimentin in non-resistant cells (see Office Action, *Claim Rejections*, pg. 3). Applicant respectfully traverses this rejection.

According to MPEP § 2131, a reference must contain each and every element, either explicitly or inherently described, as set forth in the claim to be an anticipatory reference. Furthermore, the elements in the reference must be arranged as required by the claim, even if the terminology is not similar (see MPEP § 2131).

Independent claim 1 is directed to a method of detecting multidrug resistance or multidrug resistance potential in a test neoplastic cell. The method comprises the step of measuring a level of cell *surface-expressed* vimentin protein in the test neoplastic cell of a given origin or cell type and comparing the level of expression of cell surface vimentin in the test neoplastic cell to the level of cell *surface-expressed* vimentin protein in a nonresistant neoplastic cell of the same origin or cell type. The presence of multidrug resistant potential is indicated if the level of cell *surface-expressed* vimentin in the test neoplastic cell is greater than the level of cell *surface-expressed* vimentin in the nonresistant neoplastic cell of the same given origin or cell type.

Applicants respectfully assert that the references identified by the Examiner each lack one or more elements of the claims. In particular, the references do not disclose the step of detecting the level of expression of cell *surface-expressed* vimentin on a neoplastic cell. Therefore, none of the references presented qualify as anticipatory prior art under 35 U.S.C. §102(b).

In particular, Applicants respectfully disagree with the Examiner's interpretation of the Meschini reference. Applicants assert that the Meschini reference does not disclose the step of detecting the level of expression of cell *surface-expressed* vimentin. In the Meschini reference, the authors measure the *intracellular* level of expression vimentin in a neoplastic cell. The authors describe permeabilizing the neoplastic cell membranes in preparation for vimentin labeling (see Meschini *et al.*, pg. 617). It should be noted that this process is used to increase the accessibility of the *intracellular* components to extracellular macromolecules such as antibodies. The staining shown in Figure 2 for vimentin is similar to that shown for cytokeratin, which the authors explicitly state is associated with filaments that are disposed *within* the cell (see pg. 618; and Figs. 2 and 3). Accordingly, Applicants respectfully assert that the Meschini reference does not disclose the detection of cell *surface-expressed* vimentin, and therefore does not anticipate Claim 1. Likewise, dependent claims 3-4, and 8, which contain all of the elements of claim 1, are also not anticipated by Meschini *et al.*

Accordingly, it is respectfully requested that the rejection of claims 1, 3-4, and 8 be reconsidered and withdrawn.

In addition, claims 1-4 and 6-9 were rejected as being anticipated by Bichat *et al.* (1997) *Anticancer Res. Treat.* 17: 3393-3402. Applicants respectfully traverse this rejection.

Claim 1 has been described above.

The Examiner opines that the Bichat reference teaches (1) the detection of cell surface-expressed vimentin in drug-resistant neoplastic cells, and (2) the comparison of the level of expression of cell surface-expressed vimentin in drug-resistant cells to the level of expression of cell surface-expressed vimentin in non-resistant cells (see Office Action, *Claim Rejections*, pg. 4).

Applicants respectfully disagree with the Examiner's interpretation of this reference. Applicants aver that the Bichat reference teaches the detection of *intracellular* vimentin expression. As an initial matter, the authors state that vimentin expression had been found *intracellularly* around the nucleus and *in the cytoplasmic compartment* (see Bichat *et al.*, pp. 3397-3398). The authors make no mention of cell *surface-expressed* vimentin. Moreover, the authors state that Western blots were performed on cytoskeleton extracts, which are derived from the cytoplasm, not the cell surface (see Bichat *et al.*, pg. 3396, Fig. 4B).

Therefore, Applicants respectfully assert that the Bichat reference does not disclose the step of *detecting cell surface-expressed vimentin* as required by claim 1, and so is not anticipatory. Likewise, claims 3, 4, and 6-9, which are dependent on claim 1, and thus contain all of the limitations thereof, are not anticipated by Bichat *et al.*

Accordingly, it is respectfully requested that this § 102 rejection be reconsidered and withdrawn.

Further, claims 59, 61-62, and 64-65 were rejected as being anticipated by Essa *et al.* (1996) *J. Egypt. Soc. Parasit.* 26: 433-442 or Thomas *et al.* (1999) *Clin. Cancer Res.* 5: 2698-2703. Applicants respectfully traverse this rejection.

Claim 59 is directed to a method for detecting whether a test cell is neoplastic. The method comprises the steps of first measuring a level of cell surface expressed vimentin protein in the test cell, and second comparing that level of cell surface vimentin expression to the level of cell *surface-expressed* vimentin in a nonneoplastic cell of the same origin as the test neoplastic cell. The presence of a neoplastic cell is indicated if the test cell has a higher level of cell *surface-expressed* vimentin than the nonneoplastic cell.

The Examiner alleges that the Essa reference discloses that vimentin is preferentially expressed in tumor cells as compared to epithelial cells (see Office Action, *Claim Rejections*, pg. 4). In addition, the Examiner opines that the Thomas reference teaches a method of predicting the severity of breast cancer utilizing fluorescently labeled antibodies directed against vimentin (see Office Action, *Claim Rejections*, pg. 5).

Applicants aver that the Essa *et al.* reference does not disclose the step of *detecting cell surface-expressed vimentin* as recited in Claims 59, 61-62, and 64-65. The Essa reference teaches comparing the levels of vimentin expression identified in paraffin-embedded sections of whole neoplastic tissues to the levels of vimentin expression identified *within* epithelial cells (see Essa *et al.*, pg. 438). The authors have not assessed the levels of *cell surface-expressed* vimentin using this technique, but have merely determined the level of vimentin expression throughout the cell. Thus, the amount of *cell surface-expressed* vimentin cannot be determined from the teachings of Essa *et al.*

Likewise, Applicants assert that the Thomas *et al.* reference does not disclose the step of *detecting the levels of expression of cell surface-expressed vimentin,* which is an element of Claim 59. The Thomas reference merely establishes the prognostic value of using vimentin and keratin expression generally to determine the aggressiveness of certain breast cancers (see Thomas *et al.*, pg. 2702). The Thomas reference does not teach that vimentin expression is being detected on the cell surface, in particular. To the contrary, the authors identified vimentin expression in association with intermediate filaments located *within* the cell using radiolabeled antibodies (see Thomas *et al.*, Figs. 1B and 1C, pg. 2700). This reference also does not establish that *cell surface expression of vimentin* is prognostic of cancer.

Thus, Applicants respectfully aver that as neither the Thomas reference nor the Essa reference teaches Applicants' claimed method of detecting *cell surface-expressed vimentin*, these references do not anticipate claim 59. Furthermore, claims 61-61 and 64-65, all of which depend from claim 59, contain all of the elements of claim 59, and likewise are not anticipated by the cited references.

Accordingly, Applicants respectfully request that this § 102 rejection be reconsidered and withdrawn.

3. Claim Rejections Under U.S.C. § 103

Claims 1-9 were rejected as being unpatentable over Bichat *et al.* in view of Goldenberg *et al.*, (U.S. Patent No. 4,444,744). Applicants respectfully traverse this rejection.

For a claimed invention to be obvious under 35 U.S.C. § 103, the references forming the basis for an obviousness rejection must teach or suggest all of the claim limitations of the claimed invention. (*In re Royka*, 490 F.2d 981 (C.C.P.A. 1974)).

Applicants' claim 1, directed to a method of detecting multidrug resistance by detecting cell *surface-expressed* vimentin, is described above.

Bichat *et al.* teaches the detection of *intracellular* vimentin expression, particularly teaching that vimentin expression is found intracellularly around the nucleus and in the cytoplasmic compartment (see Bichat *et al.*, pp. 3397 and 3398). The Bichat *et al.* reference does not teach or suggest that vimentin expression is found at the *cell surface*.

The Goldenberg *et al.* reference teaches generally the use of radiolabeled antibodies to detect proteins in tumors. This reference does not teach or suggest the detection of vimentin on or in cells. Thus, neither of the references cited in the Office Action teach nor suggest the detection of *cell surface-expressed vimentin,* alone or in combination, for measuring multidrug resistance.

Likewise, claims 2-9, which are dependent from claim 1 and contain all of the limitations thereof, are not obviated by these references.

Accordingly, Applicants respectfully request that this § 103 rejection be reconsidered and withdrawn.

Claims 59-65 were rejected as being unpatentable over Thomas *et al.* in view of Bichat *et al.*, and Goldenberg *et al.* Applicants respectfully traverse this rejection.

As stated above, for a claimed invention to be obvious in light of the prior art, the references forming the basis for an obviousness rejection must teach or suggest all of the claim limitations of the claimed invention. (*In re Royka*, 490 F.2d 981 (C.C.P.A. 1974)).

Applicants' claim 59, directed to a method of detecting whether a test cell is neoplastic by detecting a level of cell *surface-expressed* vimentin, has been described above.

As described above, Thomas *et al.* teaches using vimentin expression as detected in paraffin sections of whole tissues isolated from cancer patients, including *intracellular* vimentin expression, for cancer prognosis. This reference does not teach or suggest the detection of *cell surface-expressed* vimentin, nor that *surface-expressed* vimentin is indicative of neoplasty.

As described above, the Bichat *et al.* reference teaches the detection of *intracellular* vimentin expression around the nucleus and in the cytoplasmic compartment (see Bichat *et al.*, pp. 3397 and 3398). The Bichat *et al.* reference does not teach or suggest that vimentin expression is found at the cell surface, nor that *surface-expressed* vimentin is indicative of neoplasty or is a measure of neoplastic potential.

As described above, the Goldenberg *et al.* reference teaches the use generally of radiolabeled antibodies to detect proteins in tumors. Its teaching is limited to the use of radiolabeled antibodies to detect protein expression in cancer cells and does not teach or suggest the detection of vimentin at all. Neither does the Goldenberg reference teach or suggest that *surfaced-expressed* vimentin is indicative of neoplasty or is a measure of neoplastic potential.

None of the references cited in the Office Action teach or suggest the detection of cell *surface-expressed* vimentin, alone or in combination. Therefore, the combination of these references does not result in Applicants' claim 59.

Likewise, claims 60-65, which are dependent on claim 59, and thus contain all the limitations thereof, are also not obviated by the combination of these references.

Accordingly, Applicants respectfully request that this § 103 rejection be reconsidered and withdrawn.

In addition, claims 10, 12, and 14-19 were rejected as being unpatentable over Bichat *et al.* in view of Heidenthal *et al.* ((2000) *Biochem. Biophys. Res. Comm.* 267: 49-53) and Fanger *et al.* (U.S. Patent No. 5,762,930). Applicants respectfully traverse this rejection.

As discussed above, for a claimed invention to be obvious in light of the prior art, the references forming the basis for an obviousness rejection must teach or suggest all of the claim limitations of the claimed invention. (*In re Royka*, 490 F.2d 981 (C.C.P.A. 1974)).

Claim 10 is directed to a method of detecting a multidrug resistant cell in a patient by administering to the patient a vimentin binding agent and detecting a level of expression of cell *surface-expressed* vimentin by detecting the level of a vimentin binding agent bound to cell *surface-expressed* vimentin.

The Bichat *et al.* reference has been discussed above.

The Heidenthal *et al.* reference teaches that modified-LDL is bound and retained by vimentin (see Heidenthal *et al.*, pg. 52). This reference does not teach that vimentin can be located on the exterior surface of a tumor cell, nor that cell *surface-expressed* vimentin is prognostic of multidrug resistance.

The Fanger *et al.* reference teaches the administration of labeled LDL to patients. The Fanger *et al.* reference does not teach or suggest the use of labeled LDL to detect *cell surface-expressed* vimentin tumor cells or that *surface-expressed* vimentin is indicative of multidrug resistance.

None of the references cited in the Office Action teach or suggest the detection of cell *surface-expressed* vimentin, alone or in combination. The Bichat *et al.* reference does not teach the detection of *cell surface-expressed* vimentin. Similarly, the Heidenthal *et al.* reference does not teach or suggest the detection *cell surface-expressed* vimentin. To the contrary, the authors state that vimentin binding may be occurring *within* the cell, indicating that the authors are unaware of the location of vimentin as it binds to modified LDL (Heidenthal *et al.*, pg. 52). In addition, the Fanger *et al.* reference is limited to the administration of labeled LDL to patients, and does not teach or suggest the use of labeled LDL to bind to *cell surface-expressed* vimentin, nor that *surface-expressed* vimentin is a measure of multidrug resistance of a tumor.

Thus, the combination of these references does not result in all the elements of claim 59. Likewise, claims 12 and 14-19, which are dependent on claim 10 and, thus, contain all the limitations thereof, are not obviated by the combination of the cited references.

Accordingly, Applicants respectfully request that this § 103 rejection be reconsidered and withdrawn.

In addition, claims 66, 68, and 70-74 were rejected as being unpatentable over Essa *et al.* in view of Heidenthal *et al.* ((2000) *Biochem. Biophys. Res. Comm.* 267: 49-53) and Fanger *et al.* (U.S. Patent No. 5,762,930). Applicants respectfully traverse this rejection.

As described above, for a claimed invention to be obvious in light of the prior art, the references forming the basis for an obviousness rejection must teach or suggest all of the claim limitations of the claimed invention. (*In re Royka*, 490 F.2d 981 (C.C.P.A. 1974)).

Applicants' claim 66 is directed to a method for detecting neoplasty in a patent.

Also described above, Essa *et al.* reference teaches comparing the levels of vimentin expression identified in paraffin-embedded sections of whole neoplastic tissues to the levels of vimentin expression identified *within* epithelial cells (see Essa *et al.*, pg. 438). The Essa *et al.* reference does not teach or suggest the detection of *cell surface-expressed* vimentin, alone. Neither does this reference teach that *surface-expressed* vimentin is indicative of neoplasty.

The Heidenthal *et al.* reference merely teaches that modified-LDL is bound and retained by vimentin (see Heidenthal *et al.*, pg. 52). The reference does not teach that vimentin is located on the exterior surface of the cell, nor that *cell surface* vimentin expression is at all indicative of neoplasty.

The Fanger *et al.* reference teaches the administration of labeled LDL to patients. This reference does not teach or suggest the use of labeled LDL to detect *cell surface-expressed* vimentin tumor cells, nor that *cell surface* expression is at all indicative of neoplasty.

None of the references cited in the Office Action teach or suggest the detection of cell *surface-expressed* vimentin, nor that *surface-expressed* vimentin is indicative of neoplasty. Accordingly, the combination of these references does not obviate claim 66.

Likewise, claims 68 and 70-74, which are dependent on claim 66 and, thus, contain all of the limitations thereof, are not obviated by the combination of these references.

Accordingly, Applicants respectfully request that this § 103 rejection be reconsidered and withdrawn.

CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully submit that the outstanding rejections contained in the Office Action mailed on September 21, 2005 should be reconsidered and withdrawn.

No fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner believes that any further discussion of this communication would be helpful, please contact the undersigned at the telephone number provided below.

Respectfully submitted,

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